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Hypromellose (HPMC) Capsule Shells — Specification

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Food Additives Sectional Committee, FAD 08

FOREWORD

This Indian Standard was adopted by the Bureau of Indian Standards, after the draft finalized by the Food Additives Sectional Committee had been approved by the Food and Agriculture Division Council.

In recent era, plant origin capsules are new approach which might replace the usage of gelatin or non-plant origin capsules. Modified naturally occurring polymers of cellulose are considered safe for normal consumption, in human. Hydroxypropyl methyl cellulose (HPMC) most commonly known as hypromellose is mainly used in manufacturing of such kind of capsule shell.

Most of pharmaceutical capsules available in market are made of gelatin; however several HPMC capsules for powdered herbs and dietary supplements have come up in recent years. The cross linking of gelatin and drug incompatibilities and the strict regulations regarding the use of animal derived gelatin requiring the absence of bovine spongiform encephalopathy (BSE) have encouraged the search for gelatin replacement. Religious, cultural and personal issues may affect patients preference towards the medications presented in capsule dosage forms. Hypromellose (HPMC) capsules are good alternative of gelatin capsules due to its plant source. The aim of this specification on the Hypromellose (HPMC) Capsule Shells is as a replacement for hard gelatin capsules.

In the formulation of this standard, due consideration has been given to the provisions of the *Food Safety and Standards Act*, 2006 and the *Rules* and *Regulations* framed thereunder and the *Legal Metrology (Packaged Commodities) Rules*, 2011. However, this standard is subject to the restrictions imposed under these, wherever applicable.

For the purpose of deciding whether a particular requirement of this standard is complied with, the final value, observed or calculated, expressing the result of a test or analysis shall be rounded off in accordance with IS 2 : 1960 'Rules for rounding off numerical values (*revised*)'. The number of significant places retained in the rounded off value should be the same as that of the specified value in this standard.

Indian Standard

HYPROMELLOSE (HPMC) CAPSULE SHELLS — SPECIFICATION

1 SCOPE

This standard covers the requirements and test methods of hard hypromellose (HPMC) capsule shells used for encapsulation of drugs, herbs, nutritional supplements or similar products.

2 REFERENCES

The standards given below contain provisions which, through reference in this text, constitute provisions of this standard. At the time of publication, the editions indicated were valid. All standards are subject to revision and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of these standards:

IS No.	*Title*
1699 : 1994	Methods of sampling and test for food colours
2491 : 2013	Food hygiene — General principles — Code of Practice
4905 : 1968	Methods for random sampling
5191 : 1903	Sodium alginate, food grade
5306 : 1996	Sodium carboxymethyl cellulose, food grade
5403 : 1999	Method for yeast and mould count of foodstuffs and annimal feeds
5707 : 1996	Agar, food grade
5887	Methods for detection of bacteria responsible for food poisoning
(Part 1) : 1976	Isolation, identification and enumeration of *Escherichia Coli*
(Part 2) : 1976	Isolation, identification and enumeration of *Staphylococcus Aureus* and *Faecal Streptococci*
(Part 3) : 1999	General guidance on methods for detection of *Salmonella*
6795 : 2007	Acacia (Arabic) gum, food grade
7237 : 1997	Carob bean gum, food grade
7238 : 1997	Tragacanth gum, food grade
7239 : 2007	Gum ghatti, food grade
7928 : 1992	Alginic acid, food grade
10502 : 1993	Guar gum, food grade
12408 : 1998	Gum karaya, food grade
15929 : 2012	Pectin, food grade — Specification
16147 : 2014	Carrageenan, food grade — Specificaion

3 SIZE DESIGNATION

Hypromellose capsule (HPMC) shells shall be manufactured in 8 size designations with the average weights as given in Table 1. In addition sizes other than the ones given below may be manufactured as decided between the supplier and the purchaser.

Table 1 Average Weight of HPMC Shells

(*Clause* 3)

Size Designation	000	00	0	1	2	3	4	5
Range of Average Weight, mg	147 to 182	115 to 140	92 to 114	70 to 86	58 to 72	45 to 55	35 to 44	25 to 33

3.1 The testing of average weight shall be done as per the methods given in Annex A.

4 REQUIREMENTS

4.1 Description

4.1.1 Hypromellose capsule (HPMC) shells shall consist of two parts; the cap and the body. Both are open at one extreme. Other extreme of both is hemispherical.

4.1.2 It shall be smooth, glossy and clean. The cap shall overlap the body and maintains a closure in such a manner that it shall not detach during handling.

4.1.3 It shall be free from any extraneous matter, unpleasant odour and surface defects. List and descriptions of the defects are given in Annex B. The critical, major and minor defects (as defined in Annex B) shall not be more than as given in Table 3.

4.1.4 It shall pass the identification test for HPMC as given in Annex C.

4.2 Composition

The main composition of hypromellose capsule (HPMC) shells are HPMC and water.

NOTE — HPMC shall not be from genetically modified source.

4.2.1 In addition it may contain the following as permitted under the *Indian Pharmacopoeia or FSSAI Regulations*.

4.2.1.1 *Gelling agents*

A suggested list of gelling agents is given below which is not an exhaustive list and is for guidance only:

a) Carrageenan (*see* IS 16147),

b) Sodium alginate, food grade (*see* IS 519),
c) Agar, food grade (*see* IS 5707),
d) Acacia (Arabic) gum, food grade (*see* IS 6795),
e) Carob bean gum, food grade (*see* IS 7237),
f) Tragacanth gum, food grade (*see* IS 7238),
g) Gum ghatti, food grade (*see* IS 7239),
h) Guar gum, food grade (*see* IS 10502),
j) Gum karaya, food grade (*see* IS 12408),
k) Gellan gum,
m) Pectin (*see* IS 15929), and
n) Xanthan gum.

4.2.1.2 *Preservatives*

Only permitted preservatives in the quantities as per *Food Safety and Standards (Food Product Standards and Food Additives) Regulations*, 2011 shall be used.

4.2.1.3 *Colours*

Only permitted food colours as given in the *Food Safety and Standards (Food Product Standards and Food Additives) Regulations*, 2011 or the *Indian Pharmacopoeia,* 2014 shall be used. Quantity added shall be as per the provisions of these regulations. For use with drugs, the colours as permitted by *Drug & Cosmetic Acts*, 1940 and *Rules*, 1945 shall be permitted and if used for food applications it shall be as per the *Food Safety and Standards (Food Product Standards and Food Additives) Regulations*, 2011.

4.2.1.4 *Flavours*

Only permitted flavours in the quantities as per *Food Safety and Standards (Food Product Standards and Food Additives) Regulations*, 2011 shall be used.

4.2.1.5 *Lubricants*

Any food or pharma grade material may be used.

4.2.1.6 *Disintegrants*

Any food or pharma grade material may be used.

4.2.1.7 Titanium dioxide as opacifying agent as per GMP.

4.3 Hygienic Conditions

The product shall be manufactured and packed under hygienic conditions (*see* IS 2491).

4.4 Disintegration of Material

Hypromellose capsule (HPMC) shells shall comply with the disintegration test when tested as per the method given in Annex D.

4.5 Microbiological Requirements

4.5.1 *Escherichia coli* shall be absent in 1g of the sample when tested in accordance with the method given in IS 5887 (Part 1).

4.5.2 *Staphylococcus aureus* shall be absent in 1g sample when tested in accordance with the method given in IS 5887(Part 2).

4.5.3 *Pseudomonas aeruginosa*, shall be absent in 1g sample when tested in accordance with the method given in Annex E.

4.5.4 *Salmonella* shall be absent in 10g sample when tested in accordance with the method given in IS 5887 (Part 3).

4.5.5 Yeast and mould, shall not exceed 100/g when tested in accordance with the method given in IS 5403.

4.5.6 The total viable colony count shall not exceed 1 000/g at 37±1°C when tested in accordance with the methods given in IS 5402.

4.6 HPMC capsule shells shall also comply to the requirements as given in Table 2.

Table 2 Requirments for HPMC Capsule Shells

(*Clause* 4.6)

Sl No. (1)	Characteristic (2)	Requirement (3)	Method of Test (4)
i)	Loss on drying, percent by mass, *Max*	9.0	Annex F of IS 5306
ii)	Total ash, percent by mass, *Max*:		**A-4** of IS 7928
	a) For food applications	7.0	
	b) For pharmaceutical applications	10.0	
iii)	Acid insoluble ash, percent by mass, *Max*	0.5	**A-5** of IS 7928
iv)	Lead (as Pb), mg/kg, *Max*	10	**15** of IS 1699
v)	Arsenic (as As), mg/kg, *Max*	3	**15** of IS 1699
vi)	Chromium (as Cr), mg/kg	2	**15** of IS 1699
vii)	Mercury (as Hg), mg/kg, *Max*	0.5	**15** of IS 1699
viii)	Cadmium (as Cd), mg/kg, *Max*	1	**15** of IS 1699
ix)	Heavy metals (as Pb), mg/kg	40	**16** of IS 1699
x)	Lubricant content, percent by mass, *Max*	0.5	Annex F

NOTE — Established methods of test by inductively coupled plasma spectrophotometer as given in national pharmacopeia like IP/USP/BP may also be used to test the requirements as given in Sl No. (iv) to (ix). In case of dispute, the method given in col 4 shall be the reference method.

5 PACKING, STORAGE AND MARKING

5.1 Packing

The material shall be securely packed in well filled containers with minimum access to air. The containers shall be such as to preclude contamination of the contents with metals or other impurities. The quantity of material in each packaged shall be as decided between the supplier and the customer.

5.2 Storage

The material shall be stored in a cool and dry place so as to avoid excessive exposure to moisture and heat. The conditions for storage of hypromellose capsule shells shall be as follows:

a) Temperature : 15 to 30°C
b) Humidity : 40 to 65 percent RH

5.3 Marking

Each container shall be legibly and indelibly marked with the following information:

a) Name of the material;
b) Name and address of the manufacturer;
c) Batch or Code No;
d) Size designation of the capsule shell;
e) Net quantity when packed;
f) Instruction for storage;
g) Best before date (month and year to be given by the manufacturer); and
h) Any other requirements as specified under the *Legal Metrology (Packaged Commodities) Rules,* 2011and *Food Safety and Standards (Packaging and Labelling) Regulation*, 2011and the Rules framed thereunder.

5.3.1 *BIS Certification Marking*

The product may also be marked with the Standard Mark.

5.3.2 The use of the Standard Mark is governed by the provisions of the *Bureau of Indian Standards Act*, 1986 and the Rules and Regulations made thereunder. The details of conditions under which the licence for the use of the Standard Mark may be granted to manufacturers or producers may be obtained from the Bureau of Indian Standards.

6 SAMPLING

The representative samples of the material shall be drawn according to the method prescribed in Annex G.

ANNEX A

AVERAGE WEIGHT

(*Clause* 3.1)

A-1 APPARATUS

A-1.1 Analytical Balance, of least count of 0.000 1g.

A-2 PROCEDURE

Take a glass plate/dish and dry it in an oven at 105 ± 2°C and then cool it in a dessicator. Weigh the dried glass plate/dish. Take 100 numbers of assembled capsules sampled randomly and weigh it together with the glass plate/dish in the balance. Calculate the average weight of the assembled capsule as follows:

$$\frac{W_2 - W_1}{100}$$

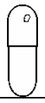
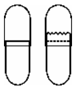
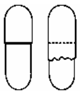
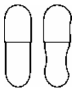
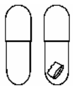
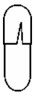
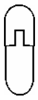
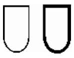
where

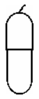
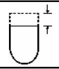
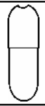
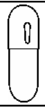
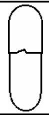
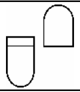
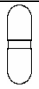
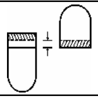
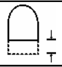
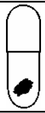
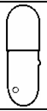
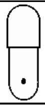
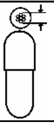
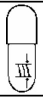
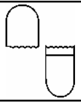
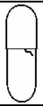
W_2 = weight of glass plate/dish with capsules, and
W_1 = weight of dried empty glass plate/dish.

ANNEX B

(*Clause* 4.1.3)

LIST AND DEFINITIONS OF SURFACE DEFECTS

Category (1)	Visual Defect (2)	Description (3)
Critical Defect		Hole – It is a capsule, which has been pierced on any part of its surface.
		Uncutbody – It is a capsule whose body has not been cut. The length becomes more by 3 to 5 mm than nominal length.
		Uncutcap – It is a capsule whose cap has not been cut. The length becomes more by 3 to 5 mm than nominal length.
		Mashed – It is a capsule, which is totally deformed or crumpled.
		Trims (Loose Ring Outside) – It is surplus shell from the dipping resulting from cutting of the shell. It can be from cap or body.
Critical Deffect		Trims (Loose Ring Inside) – It is a capsule, which has loose ring inside the joined shells. It can be from cap or body.
		Split (Rapid Dried) – It is a capsule having longitudinal break in film straight or spiral, from the edge of cap or body cut end. Critical defect (if the cut is more than1 mm).
		Telescoped – It is a capsule whose body is partially cut and come out of cap during joining.
		Double Dip – Double dip is the shell which got dipped twice, hence has high Weight, SWT, Dome, etc.

Category (1)	Visual Defect (2)	Description (3)
		String on End – It is a capsule whose either cap or body has excess gelatin in the form of string near dome.
		Short Body – Length of body shorter by 2 mm than nominal length.
Major Deffect		Punched End (Dented) – It is a capsule whose either cap or body has inverted dome. Major defect (if the indentation is more than 2 mm diameter).
		Collet Pinch – It is a capsule whose either cap or body has longitudinal pinch generated by collet. Major defect (if the pinch is more than 3 mm in length).
		Rough Cut – It is a capsule whose either cap or body has irregular cut causing abnormal resistance for separation or causing loading problem during filling.
		Loose Piece – It is a cap or body, which are cut to the length but are found in unjoinned state.
		Double Cap – It is a joined capsule, which has two caps.
		Long Cap / Body – Length of cap or body longer by 1 mm than nominal length.
		Short Cap – Length of cap shorter by 1 mm than nominal length.
Minor Deffect		Dirty – It is a capsule on which marks can be recognized at a distance of 30 cm under natural light with an area of 3 m.
		Bubbles – It is a capsule having bubble either on cap or body having diameter more than 1 mm.
		Specks – It is a capsule having speck either on cap or body having diameter more than 1 mm.
		Strand – It is a capsule whose either cap or body has top stellated wrinkles greater than 3 mm diameter.
		Wrinkles – It is a capsule whose either cap or body has longitudinal wrinkles greater than 3mm x 2 mm.
		Uneven Cut – It is a capsule whose either cap or body has uneven cut.
		String (Spiral Cut) – It is a capsule whose either cap or body has a string generated due to spiral cutting at the cutting edge. Major defect (If length of string is more than 2 mm).

ANNEX C

(*Clause* 4.1.4)

TESTS FOR IDENTIFICATION OF HPMC

C-1 REAGENTS

C-1.1 Acetic Acid (10 Percent *w/v*)

C-1.2 Tannic Acid (10 Percent *w/v*)

C-1.3 Toluene

C-1.4 Ethanol

C-1.5 Ammonia Solution (10 Percent *w/v*)

C-2 PROCEDURE

C-2.1 Preparation of Test Solution

Take about 1g of the capsule shell material in a glass beaker and add distilled water maintained at 70 to 80°C gradually till until the aqueous layer does not have more than faint colour. Decant the aqueous layer. Dissolve the residue of capsules with 50 ml of carbon dioxide free water and make up the volume in a volumetric flask upto 100 ml with carbon dioxide free water at room temperature and stir until dissolution is complete. Filter it about 20 to 25 ml using 0.45µ membrane filter paper or any other suitable filter paper which obtain turbidity free solution.

C-2.2 Tests of Identification

C-2.2.1 Heat 10 ml of the test solution in a water bath while stirring. At temperature above 50°C the solution becomes cloudy or a flocculent precipitate is formed. The solution becomes clear again on cooling.

C-2.2.2 To 10 ml of test solution obtain from Test No. 1, add 0.3 ml of dilute acetic acid 10 percent (*w*/*v*) add 2.5 ml of 10 percent (*w*/*v*) solution of tannic acid. A flocculent precipitate is formed which dissolves in dilute ammonia solution (10 percent *w*/*v*).

C-2.2.3 Place 1 ml of the test solution on a glass plate. Evaporate over a hot plate. After evaporation of the water a thin film is formed.

C-2.2.4 0.2 g of capsule shell does not dissolve in 10 ml of toluene or in 10 ml of ethanol.

ANNEX D

(*Clause* 4.4)

DISINTEGRATION TEST FOR CAPSULE

D-1 For the purpose of this test, disintegration does not imply complete solution of the dosage unit or even of its active constituent. Disintegration is defined as that state in which no residue of the unit under test remains on the screen of the apparatus or, if a residue remains, it consists of fragments of disintegrated parts of tablets component parts such as insoluble coating of the tablets or of capsule shells, or of any melted fatty substance from the pessary or suppository or is a soft mass with no palpable core. If discs have been used with capsules, any residue remaining on the lower surfaces of the discs consists only of fragments of shells.

D-2 Medium

Use water.

D-3 Apparatus

The apparatus consists of a basket-rack assembly, a 1litre beaker, a thermostatic arrangement for heating the fluid and a mechanical device for raising and lowering the basket in the immersion fluid at a constant frequency rate.

D-3.2 Basket-Rack Assembly

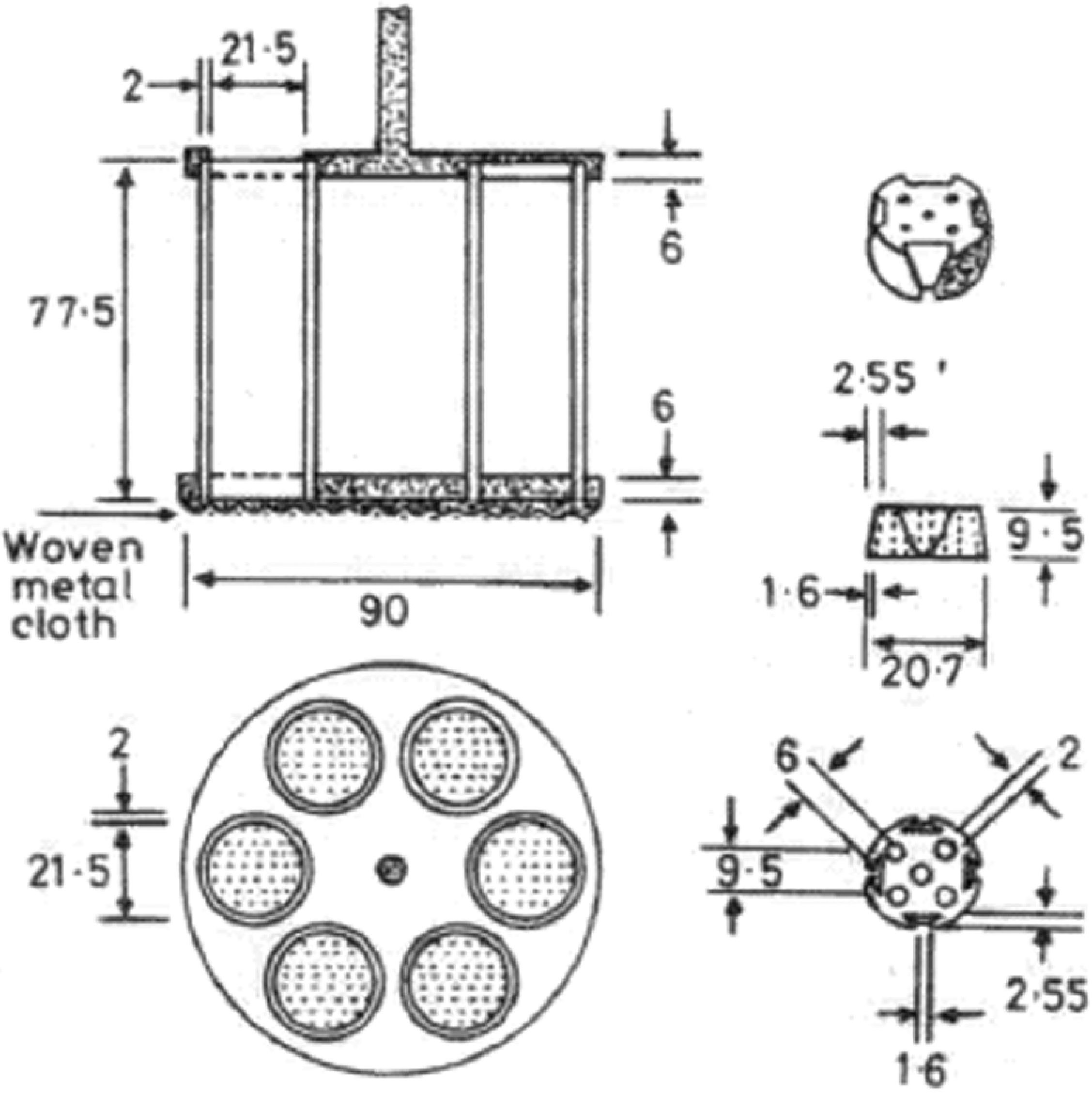
The basket-rack assembly is rigid and supports six cylindrical glass tubes, 77.5 ± 2.5 mm long, 21.5 mm in internal diameter and with a wall thickness of about 2 mm (*see* Fig. 1). The tubes are held vertically by two superimposed transparent plastic plates, 90 ± 2 mm in diameter and 6.75 ± 1.75 mm thick perforated by six holes having the same diameter as the tubes. The holes are equidistant from the centre of the plate and are equally spaced from one another. Attached to the underside of the lower plate is a woven stainless steel wire cloth with a plain square weave with 2.0 ± 0.2 mm mesh apertures and with a wire diameter of 0.615 ± 0.045 mm. The upper plate is covered with a stainless steel disc perforated by six holes, each about 24 ± 2 mm in diameter, which fits over the tubes and holds them between the plastic plates. The holes coincide with those of the upper plastic plate and the upper open ends of the glass tubes. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

D-3.2.1 The plates are held rigidly in position and 77.5 mm apart by vertical metal rods at the periphery and a metal rod is also fixed to the centre of the upper plate to enable the assembly to be attached to the device for raising and lowering it smoothly at a constant frequency of between 28 and 32 cycles/min through a distance of 50 to 60 mm. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction should be smooth and not abrupt. There should be no appreciable horizontal motion or movement of the axis from the vertical.

D-3.2.2 The design of the basket-rack assembly may be somewhat different provided specifications for the glass tubes and the screen mesh size are unchanged.

D-3.2.3 *Discs*

A cylindrical disc for each tube, each 20.7 ± 0.15 mm thick in diameter and 9.5 ± 0.15 mm thick, made of transparent plastic whit a relative density of 1.18 to 1.20, and pierced with five holes, each 2 mm in diameter, one in the centre and the other four spaced



All dimensions in millimetres.

FIG 1

equally on a circle of radius 6 mm from the centre of the disc. Four equally-spaced grooves are cut in the lateral surface of the discs in such a way that at the upper surface of the disc they are 9.5 mm wide and 2.55 mm deep and at the lower surface 1.6 mm^2.

D-3.2.4 *Medium*

The assembly is suspended in the liquid medium in a suitable vessel, preferably a 1 litre beaker. The volume of liquid is such that the wire mesh at its highest point is at least 25 mm below the surface of the liquid, and at its lower point is at least 25 mm above the bottom of the beaker. At no time should the top of the basket-rack assembly become submerged. There is a thermostatic arrangement for heating the liquid and maintaining the temperature at 37 ± 2°C.

D-3.3 Procedure

Introduce one empty cellulose capsule shells into each tube. Add a disc to each tube. Suspend the assembly in the beaker containing water. Simultaneously start the stopwatch and the disintegration test (DT) apparatus. Operate the disintegration test (DT) apparatus for 15 min. Stop the stopwatch when the last capsule disintegrates. Note down the time lapse from the start. Remove the assembly from the liquid. The capsules pass the test, if all of them have disintegrated within 15 min. If 1 or 2 empty cellulose capsules fail to disintegrate, repeat the test on 12 additional capsules shells; not less than 16 of the total of 18 capsules shells tested disintegrate in water at 35°C – 39 °C in 15 min.

ANNEX E

(*Clause* 4.5.3)

DETECTION OF PSEUDOMONAS AERUGINOSA

E-1 PSEUDOMONAS AERUGINOSA

Microorganisms capable of growth and producing a water soluble, fluorescent pigment in media containing asparagines and ethanol. They also produce characteristic colonies when grown on agar medium containing milk at 42°C. Some strains are non-pigmented.

E-2 PRINCIPLE

The sample is powdered in a sterile atmosphere and a suspension is formed in water which are added to a selective medium in containers and incubated under the conditions given for the medium. Examination of the containers either for the presence of a water-soluble fluorescing pigment under ultraviolet irradiation or for growth is done. Sub-cultures are made from each container showing growth or fluorescence on to plates of milk agar medium. After incubation, the plates are examined for typical colonies of *Pseudomonas aeruginosa*; sub-cultures are made from each container on to the surface of a solid agar plate and incubated. Pure cultures are obtained by further subculture on to plates of the same agar medium as required.

E-3 CULTURE MEDIA

Use the following culture media for the detection of *Pseudomonas aeruginosa*:

Asparagine Proline Broth	*Single Strength*	*Concentrated*
DL Asparagine	2g	3.2 g
L Proline	1 g	1.6 g
Anhydrous dipotassium hydrogen phosphate	1 g	1.6g
Magnesium sulphate heptahydrate	0.5 g	0.8 g
Anhydrous potassium sulphate	10 g	16g
Ethanol	25 ml	40 ml
Water	1 000 ml	1 000 ml

E-3.1 Preparation

Dissolve all the constituents in the water and proceed in either of the following ways:

Add the ethanol and distribute in sterile screw-capped bottles. Tighten the caps on the bottles to the point where the seal in the lid just begins to engage with the lip of the bottle, autoclave at 121 ± 1°C for 15 min. Tighten the caps on each bottle, immediately after removal from the autoclave, to prevent loss of ethanol by evaporation. Do not use polypropylene caps without seals.

Alternatively, sterilize the ethanol by filtration through a cellulose acetate or nitrate membrane of average pore size 0.22 µm and then add it aseptically to the medium after autoclaving and cooling. Adjust the *p*H to 7.2 ± 0.2. Store in screw-capped bottles in the dark at room temperature for up to a maximum of 3 months.

E-4 CONFIRMATORY MEDIUM

E-4.1 Milk Agar with Cetrimide

a)	Skim milk powder	: 100 g
b)	Yeast extracts broth	: 250 ml
c)	Agar	: 15 g
d)	Hexadecyltrimethylammonium bromide (centrimide)	: 0.3 g
e)	Water	: 750 ml

E-4.1.1 *Yeast Extract Broth*

a)	Bacteriological yeast extract	: 3g
b)	Bacteriological peptone	: 10g
c)	Sodium chloride	: 5g
d)	Water	: 1 000 ml

E-4.2 Preparation on Medium

Prepare the yeast extract broth by dissolving all the constituents in the distilled water by steaming. Adjust the *p*H between 7.2 and 7.4. Sterilize by autoclaving at 121 ± 1°C for 20 min. Mix the sterile yeast extract broth, centrimide and agar, and steam this mixture until the agar has dissolved. In a separate glass container, add the skim milk powder to the distilled water and mix, preferably with a magnetic stirrer, until the powder has completely dissolved. Autoclave both solutions separately at 121 ± 1°C for 5 min. To prevent caramelization of the milk, take care to follow these instructions. Cool the solutions to 50°C aseptically add the milk solution to the agar medium and mix well.

E-5 APPARATUS AND GLASSWARE

a) All glassware shall be sterilized at 170 ± 5°C for 1 h in a dry oven or at 121 ± 1°C for 15 min in an autoclave before use.

b) Use sterile petri-dishes with a diameter of either 90 mm or 100 mm.

c) Incubators, capable of being maintained, at 37 ± 1°C and 42 ± 0.5°C.

d) Ultraviolet lamp emitting light of wavelength 360 ± 20 nm.

E-6 INNOCULATION AND INCUBATION

Take the sample from the lot and crush it to small powder using mortar and pestle in a sterilized manner. From the powered sample take 1 g sample and add to 10 ml of sterilized distilled water in sterile bottles. Allow the sample to dissolve to form a thickened mass and then to it add 50 ml of asparagine proline broth. Incubate the bottles at 37 ± 1°C for 48 h. After 48 h observe for growth and fluorescence under UV lamp in either a darkened room or apparatus designed to exclude visible light.

E-7 CONFIRMATION

E-7.1 Milk Agar

Sub-culture a loopful of culture medium from each container showing either fluorescence or growth on to a milk agar plate (*see* **D-5**), incubate the milk agar plates at 42 ± 1°C for 24 h. Examine the plates for growth, procyanine pigment (blue-green) production, and casein hydrolysis (clearing of the milk medium around the colonies) and record the reactions.

All containers of the culture medium exhibiting either growth or fluorescence, which yield colonies (after sub-culture on milk agar plates) that either produce procyanine pigment or hydrolyse casein, shall be regarded as positive for the presence of *Pseudomonas aeruginosa*.

ANNEX F

[*Table* 2, *Sl No.* (X)]

DETERMINATION OF LUBRICANT CONTENT IN CAPSULE

F-1 REAGENTS

F-1.1 Diethyl Ether

F-2 APPARATUS

F-2.1 Conical Flask, of minimum capacity of 500 ml.

F-2.2 Steam Bath

F-2.3 Hot Air Oven

F-2.4 Analytical Balance, having least count of 0.000 1g.

F-2.5 Dessicator

F-3 PROCEDURE

Open about 10 g of empty cellulose capsule shells into cap and body. Add the opened empty cellulose capsule shells to 50 ml of diethyl ether and agitate for 5 min. Filter the diethyl ether extract through Whatman No. 1 or 41 or 42 filter paper that has previously been washed twice with 20 ml diethyl ether each time.

Transfer the filtered extract to a weighed conical flask which has been dried in hot air oven at 105 ± 2 °C and cooled in a dessicator. Re-extract the capsules by repeating the operation once more with a further 50 ml of diethyl ether. Combine the two diethyl ether extracts.

Evaporate the combined diethyl ether extracts on a water bath to dryness. Cool the flask in a dessicator and weigh. If the weight of the residue (lubricant) is out of the prescribed limit for the lubricant content in the empty Cellulose capsule shells, again dry the residue on water bath for 1 h and then cool it in desiccators. Repeat drying and weighing until the difference between the two consecutive weights is less than 0.5 mg.

Perform a blank by carrying out steps as above but omitting the empty cellulose capsule shells. Deduct the weight of the blank residue, if any from the weight of the residue of the sample.

Calculate the lubricant content as follows:

$$= \frac{(W_3 - W_2) - (W_{3b} - W_{2b}) \times 100}{W_1}$$

where

W_1 = weight of empty cellulose capsule shells taken,

W_2 = weight of empty conical flask,

W_3 = weight of conical flask along with extracted and dried residue,

W_{2b} = weight of the empty conical flask used for blank determination, and

W_{3b} = weight of empty conical flask with residue of blank determination.

ANNEX G

(*Clause* 6.1)

SAMPLING AND CRITERIA FOR CONFORMITY

G-1 LOT

G-1.1 In a consignment all the hypromellose capsule (HPMC) shells, manufactured from the same size designation and belonging to the same batch of manufacture shall be grouped together to constitute a lot. Each lot shall be tested for conformity to the requirements of this standard.

G-1.2 Each lot shall be tested for conformity to the requirements of description, dimensions, average weight, disintegration time, loss on drying, ash content and acid insoluble as has given in this standard.

G-1.3 Requirements of *E. coli*, *Pseudomonas aeruginosa*, yeast and mould, total viable count and heavy metals shall be done once every day, while *Staphylococcus aureus* and *Salmonella* shall be done once in a month at a place away from the process and storage areas. Requirements of lead, arsenic, cadmium, mercury, chromium and lubricant content shall be tested once in six months or whenever, there is a change in the source/ type of raw materials.

G-2 SCALE OF SAMPLING AND CRITERIAFOR CONFORMITY

The number of hypromellose capsule (HPMC) shells to be sampled from each lot depends on the size of the lot and shall be as given in col 2 and col 3 of Table 3. These hypromellose capsule (HPMC) shells shall be selected at random making use of random number tables. For random selection procedures, reference may be made to IS 2500 (Part 4).

Table 3

(*Clause* H-2)

Sl No. (1)	**Lot Size (No. of Capsules)** (2)	**Sample Size (Visual Tests)** (3)	**Acceptance No. (Visual Tests)** (4)
i)	100 001 to 200 000	75	0 – C 0 – M 5 - m
ii)	200 000 to 500 000	200	0 – C 0 – M 10 – m
iii)	500 001 to 1 000 000	400	0 – C 0 – M 15 – m
iv)	1 000 001 to 2 000 000	800	0 – C 1 – M 20 – m
v)	2 000 001 to 5 000 000	2 000	0 – C 2 – M 30 – m

NOTE — C – critical defects, M – major defects, m – minor defects.

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